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<p>(54) Title: PHARMACEUTICALS</p> <p>(57) Abstract</p> <p>Novel oxazino[3,2-a]indole-10-carboxamide derivatives having 5-HT₄ receptor antagonist activity and useful in the treatment of gastrointestinal disorders, cardiovascular disorders and CNS disorders, including irritable bowel syndrome.</p>		

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PHARMACEUTICALS

This invention relates to novel compounds having pharmacological activity, to a process for their preparation and to their use as pharmaceuticals.

5

EP-A-429984 (Nisshin Flour Milling Co., Ltd.) describes indole derivatives having 5-HT₃ receptor antagonist activity.

European Journal of Pharmacology 146 (1988), 187-188, and Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 340:403-410, describe a non classical 5-hydroxytryptamine receptor, now designated the 5-HT₄ receptor, and that ICS 205-930, which is also a 5-HT₃ receptor antagonist, acts as an antagonist at this receptor.

WO 91/16045 (SmithKline and French Laboratories Limited) describes the use of cardiac 5-HT₄ receptor antagonists in the treatment of atrial arrhythmias and stroke.

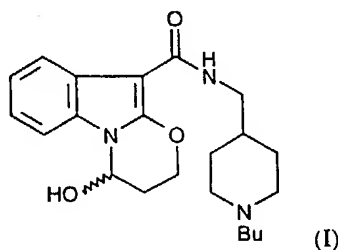
EP-A-501322 (Glaxo Group Limited) describes indole derivatives having 5-HT₄ antagonist activity.

WO93/18036 (SmithKline Beecham plc) describes certain condensed indole derivatives having 5-HT₄ receptor antagonist activity. Among these derivatives the compound N-[(1-*n*-butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-*a*]indole-10-carboxamide has been found to have potent 5-HT₄ receptor antagonist activity and to be of therapeutic value in the treatment of irritable bowel syndrome. In the evaluation of this compound we have found that one of its metabolites, namely the compound of formula (I) below, itself has potent 5-HT₄ receptor antagonist activity.

25

Accordingly, the present invention provides (±)-N-[(1-butyl-4-piperidyl)methyl]-3,4-dihydro-4-hydroxy-2H-[1,3]oxazino[3,2-*a*]indole-10-carboxamide

30 i.e. the compound of formula (I), or a pharmaceutically acceptable salt thereof:



The pharmaceutically acceptable salts of the compound of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α -keto glutaric, α -glycerophosphoric, and glucose-1-phosphoric acids.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compound of formula (I) such as the compounds quaternised by compounds R_X-T wherein R_X is C_{1-6} alkyl, phenyl- C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_X include methyl, ethyl and *n*- and *iso*-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.

The compound of the formula (I) and its pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever the compound of formula (I) or a salt thereof is herein referred to. The compound of formula (I) is a racemate. The present invention also covers the corresponding individual (+) and (-) enantiomers.

The compound of formula (I) may be prepared as described in the Example below or by other conventional coupling of the indole moiety with Z, for example by reacting 1-*n*-butyl-4-piperidinyl methylamine with (+/-)-methyl 3,4-dihydro-4-(protected)hydroxy-2H-[1,3]oxazino[3,2-*a*]indole-10-carboxylate; the 4-hydroxy group is advantageously protected by an appropriate silyl group. Suitable methods are as described in GB 2125398A (Sandoz Limited), GB 1593146A and EP-A-36269 (Beecham Group p.l.c.), EP-A-429984 (Nisshin Flour Milling Co.) and EP-A-328200 (Merck Sharp & Dohme Limited). Reference is also made to EP-A-501322 (Glaxo Group Limited). It will be appreciated that the formation of O- containing ring may be carried out before or after coupling.

Aza(bi)cyclic side chain intermediates are known compounds or may be prepared according to the methods described in PCT/GB92/01519 and /01612 (SmithKline Beecham p.l.c.).

The compounds of the present invention are 5-HT₄ receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

5 They are of potential interest in the treatment of irritable bowel syndrome (IBS), in particular the diarrhoea aspects of IBS, i.e., these compounds block the ability of 5-HT to stimulate gut motility via activation of enteric neurones. In animal models of IBS, this can be conveniently measured as a reduction of the rate of defaecation. They are also of potential use in the treatment of urinary incontinence which is often
10 associated with IBS.

They may also be of potential use in other gastrointestinal disorders, such as those associated with upper gut motility, and as antiemetics. In particular, they are of potential use in the treatment of the nausea and gastric symptoms of gastro-
15 oesophageal reflux disease and dyspepsia. Antiemetic activity is determined in known animal models of cytotoxic-agent/radiation induced emesis.

Specific cardiac 5-HT₄ receptor antagonists which prevent atrial fibrillation and other atrial arrhythmias associated with 5-HT, would also be expected to reduce occurrence
20 of stroke (see A.J. Kaumann 1990, Naumyn-Schmiedeberg's Arch. Pharmacol. 342, 619-622, for appropriate animal test method).

It is believed that platelet-derived 5-HT induces atrial arrhythmias which encourage atrial fibrillation and atrial disorders are associated with symptomatic cerebral and
25 systemic embolism. Cerebral embolism is the most common cause of ischaemic stroke and the heart the most common source of embolic material. Of particular concern is the frequency of embolism associated with atrial fibrillation.

Anxiolytic activity is likely to be effected via the hippocampus (Dumuis *et al* 1988, Mol Pharmacol., 34, 880-887). Activity may be demonstrated in standard animal
30 models, the social interaction test and the X-maze test.

Migraine sufferers often undergo situations of anxiety and emotional stress that precede the appearance of headache (Sachs, 1985, Migraine, Pan Books, London). It has also been observed that during and within 48 hours of a migraine attack, cyclic
35 AMP levels are considerably increased in the cerebrospinal fluid (Welch *et al.*, 1976, Headache 16, 160-167). It is believed that a migraine, including the prodromal phase and the associated increased levels of cyclic AMP are related to stimulation of 5-HT₄ receptors, and hence that administration of a 5-HT₄ antagonist is of potential benefit
40 in relieving a migraine attack.

The invention also provides a pharmaceutical composition comprising the compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

5

Such compositions are prepared by admixture and are usually adapted for enteral such as oral, nasal or rectal, or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, nasal sprays, suppositories, injectable and infusable solutions or
10 suspensions. Sublingual or transdermal administration is also envisaged. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and
15 contain conventional excipients such as binding agents, fillers, diluents, tableting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

20 Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

25 Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for
30 example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol;
35 preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for

reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

5

The oral compositions may be prepared by conventional methods of blending, filling or tableting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

10

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

15

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

25

The invention further provides a method of treatment of irritable bowel syndrome, gastro-oesophageal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine in mammals, such as humans, which comprises the administration of an effective amount of the compound of the formula (I) or a pharmaceutically acceptable salt thereof. In particular, the method comprises treatment of IBS or atrial arrhythmias and stroke.

30

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70 kg adult will normally contain 0.05 to 1000 mg for example 0.5 to 500 mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the

35

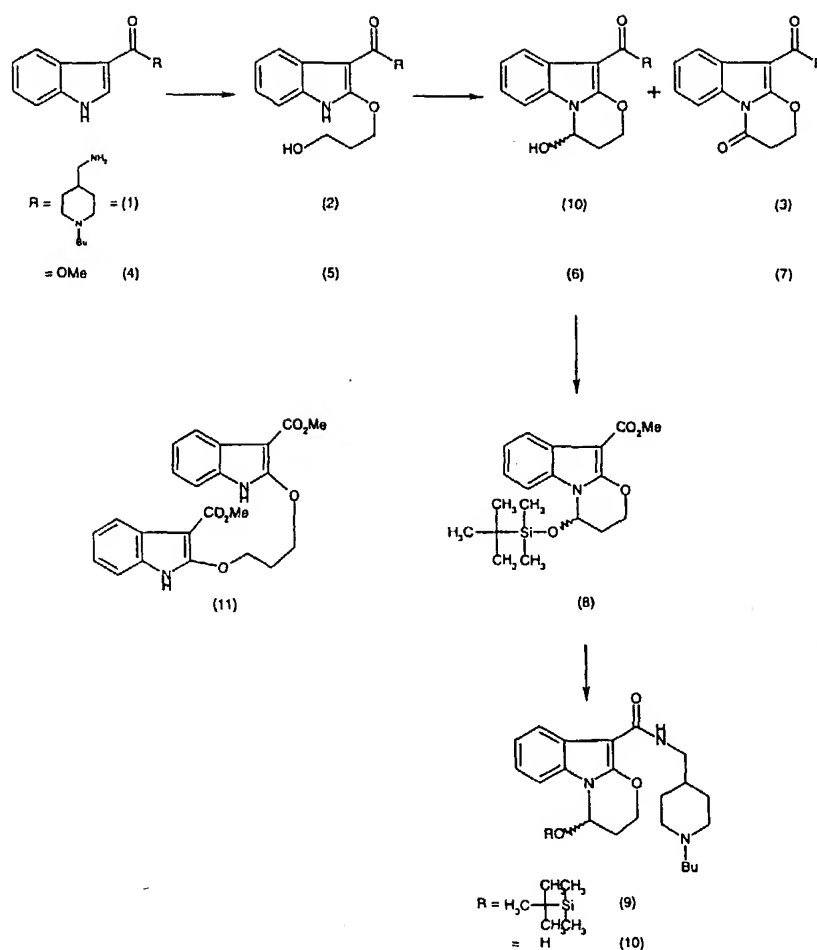
range of approximately 0.0001 to 50 mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

5 No adverse toxicological effects are indicated within the aforementioned dosage ranges.

10 The invention also provides the compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use as a 5-HT₄ receptor antagonist in the treatment of the disorders hereinbefore described.

The invention also provides the use of the compound of formula (I) in the manufacture of a medicament for use as a 5-HT₄ receptor antagonist in the treatment of the disorders hereinbefore described.

15 The following Example illustrates the preparation of the compound of formula (I) with reference to the reaction scheme below:-.



- (1) *N*-[(1-butyl-4-piperidinyl)methyl]-1*H*-indole-3-carboxamide
 (2) *N*-[(1-butyl-4-piperidinyl)methyl]-2-(3-hydroxypropoxy)-1*H*-indole-3-carboxamide
 (3) *N*-[(1-butyl-4-piperidinyl)methyl]-3,4-dihydro-4-oxo-2*H*-[1,3]oxazino[3,2-*a*]indole-10-carboxamide
 (4) methyl 1*H*-indole-3-carboxylate
 (5) methyl 2-(3-hydroxypropoxy)-1*H*-indole-3-carboxylate
 (6) methyl
 3,4-dihydro-5-hydroxy-4-oxo-2*H*-[1,3]oxazino[3,2-*a*]indole-10-carboxylate
 (7) methyl 3,4-dihydro-4-hydroxy-2*H*-[1,3]oxazino[3,2-*a*]indole-10-carboxylate
 (8) (±)-methyl 3,4-dihydro-4-[[dimethyl-(1,1-dimethylethyl)silyl]oxy]-2*H*-[1,3]oxazino[3,2-*a*]indole-10-carboxylate
 (9) (±)-*N*-[(1-butyl-4-piperidinyl)methyl]-3,4-dihydro-4-[[dimethyl-(1,1-dimethylethyl)silyl]oxy]-2*H*-[1,3]oxazino[3,2-*a*]indole-10-carboxamide
 (10) (±)-*N*-[(1-butyl-4-piperidinyl)methyl]-3,4-dihydro-4-hydroxy-

2*H*-[1,3]oxazino[3,2-*a*]indole-10-carboxamide
(11) 2,2'-propane-1,3-diylbis(oxy)bis[methyl 1*H*-indole-3-carboxylate]

The metabolite (10) was prepared a) as a mixture and b) as a pure compound:

5

Preparation a)

Preparation of (2)

To a suspension of (1) (7.62g, 0.024 mol) in chloroform (75 ml) at 5°C was added N-chlorosuccinimide (3.53g, 0.026 mol). After 30 min, 1,3-propanediol (18.5g, 0.24 mol) was added, followed by methanesulphonic acid (0.5g, 0.005 mol). The solution was stirred for a further 30 min, then washed with aqueous sodium carbonate solution (10% w/v, 50 ml). The chloroform layer was cooled to 0°C, the precipitate collected by filtration, obtaining 7.52g (80%) (2).

15 ¹H NMR (200 MHz) CD₃OD: δ: 8.05 (m,1H), 7.25 (m,1H), 7.06 (m,2H), 4.55 (t,2H), 3.8 (t,2H), 3.0 (d,2H), 2.4 (m,2H), 1.9-2.2 (m,4H), 1.3-1.9 (m,11H), 0.95 (t,3H)

Preparation of (10) as a mixture

20

To a suspension of (2) (50 mg, 0.001 mol), N-methylmorpholine-N-oxide (23 mg, 0.0015 mol), powdered 4Å molecular sieves (65 mg) in acetonitrile (2 ml) was added tetrapropylammonium perruthenate (4 mg, 0.05 mmol). The mixture was stirred for 16 hr. TLC analysis (SiO₂, MeOH) indicated metabolite (10), starting material (2), and over-oxidized diamide (3).

25

Preparation b)

Preparation of (5)

30

To a suspension of (4) (25.3g, 0.144 mol) and DABCO (8.7g, 0.078 mol) in chloroform (250 ml) at 5°C was added N-chlorosuccinimide (21g, 0.157 mol). After 30 min, 1,3-propanediol (110g, 1.45 mol) was added, followed by methanesulphonic acid (3g). The solution was allowed to warm to room temperature and stirred at room temperature for 1 hr, then washed with 10% aq. Na₂CO₃ solution, water, brine and dried (Na₂SO₄), filtered, evaporated under reduced pressure to leave an oil. Chromatography (5-50% ethyl acetate/dichloromethane) gave 16.2g (45%) (5), 3.7g (12%) dimer (11).

35

40 ¹H NMR
(5) (CD₃OD) δ: 7.85 (m,1H), 7.25 (m,1H), 7.1 (m,2H), 4.45 (t,2H), 3.85 (m,5H), 2.1 (m,2H)

(11) (d^6 DMSO) δ : 7.8 (m,2H), 7.26 (m,2H), 7.06 (m,4H), 4.55 (t,4H), 3.68 (s,6H), 2.3 (m,2H)

Preparation of (6)

5

To a mixture of (5) (4.8g, 0.19 mol), powdered 4Å molecular sieves (9.6g), N-methyl morpholine-N-oxide (3.39g, 0.029 mol) in dichloromethane/acetonitrile (10:1, 44 ml) was added tetrapropylammonium perruthenate (0.34g, 0.00097 mol). The mixture was stirred for 18 hr, filtered through celite, and the filtrate evaporated. The residue was chromatographed (0-10% ethyl acetate/dichloromethane) obtaining 1.23g (28%) (6), 0.52g (11%) (7).

10

^1H NMR (CDCl_3)

15

(6) δ : 7.8 (m,1H), 7.0-7.3 (m,3H), 5.85 (br. s, 1H), 4.4-4.73 (m,2H), 3.7 (s,3H), 2.1-2.4 (m,2H)

^1H NMR (CDCl_3)

(7) δ : 8.2 ((m,1H), 7.95 (m,1H), 7.16-7.4 (m,2H), 4.66 (t,2H), 3.86 (s,3H), 3.0 (t,2H)

20

Preparation of (8)

To a solution of (6) (2g, 0.0081 mol) and 2,6-lutidine (4.2 ml, 0.036 mol) in dichloromethane (64 ml) at -70°C was added TBDMS triflate (4 ml, 0.0174 mol) dropwise over 3 min. The solution was stirred for 1 hr, then allowed to warm to room temperature. The solution was re-cooled to -70°C , then methanol (9 ml) added dropwise over 5 min. The solution was diluted with dichloromethane (200 ml), washed with water, brine and dried (Na_2SO_4) to give an oil. This was chromatographed (10% ethyl acetate/dichloromethane to give 2g (8).

25

30

^1H NMR (CDCl_3) δ : 8.1 (m,1H), 7.2-7.31 (m,3H + CHCl_3), 6.0 (m,1H), 4.7-4.86 (m,2H), 3.95 (s,3H), 2.37-2.44 (m,1H), 2.14-2.22 (m,1H), 0.91 (s,9H), 0.29 (s,3H), 0.22 (s,3H)

Preparation of (9)

35

To a solution of 1-n-butyl-4-piperidinyl methylamine (0.95g, 0.047 mol) in toluene (2.5 ml) was added trimethylaluminium (2.3 ml, 2M in toluene, 0.046 mol) followed by (8) (1.62g, 0.045 mol) in toluene (5 ml). The solution was heated under reflux for 4 hr, then allowed to cool to room temperature and stirred with 10% aq. NaOH solution (2 ml) for 30 min. The organic layer was washed with 10% aq. NaOH solution, water, brine, dried (Na_2SO_4), filtered and the filtrate evaporated to leave an oil. This was filtered through silica, washing with ethyl acetate, then methanol obtaining 2g (89%) (9).

40

^1H NMR (CD_3OD) δ : 8.1 (m,1H), 7.3 (m,1H), 7.1 (m,2H), 6.17 (m,1H), 4.7 (m,2H), 3.0 (m,2H), 0.9-2.6 (m,29H), 0.3 (s,3H), 0.2 (s,3H)

Preparation of (10)

5

A solution of (9) (0.15g, 0.0003 mol) in water (5 ml) and glacial acetic acid (10 ml) was heated at 75°C for $6\frac{1}{2}$ hr. The solution was evaporated under reduced pressure and the residue partitioned between ethyl acetate (25 ml) and saturated aq. NaHCO_3 solution (3 ml). The ethyl acetate layer was washed with further saturated aq.

10 NaHCO_3 solution, brine, and dried (Na_2SO_4). Evaporation under reduced pressure gave (10) as a foam, 0.096g (83%) (10).

^1H NMR (CD_3OD) δ : 8.16 (m,1H), 7.5 (m,1H), 7.2 (m,2H), 6.05 (m,1H), 4.8 (m,2H), 3.4 (m,2H), 3.1 (m,2H), 1.35-2.6 (m,15H), 1.03 (t,3H) MS (M+1) 386.3

15

5-HT₄ RECEPTOR ANTAGONIST ACTIVITY

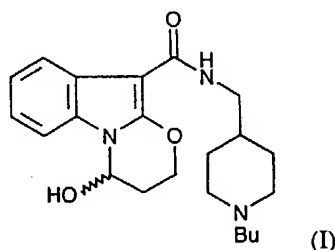
Male Dunkin Hartley guinea-pigs, weighing 200-300g are used. Longitudinal muscle-myenteric plexus (LMMP) preparations, 2-3cm long, are obtained from the distal colon region. These are suspended under a 0.5g load in isolated tissue baths containing Krebs Henseleit solution (NaCl 118mM, KCl 4.7mM KH_2PO_4 1.2mM $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ 1.2mM, Glucose 11.1mM, NaHCO_3 25mM, $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$ 2.5mM) bubbled with 5% CO_2 in O_2 , maintained at 37°C and containing 1 μM Granisetron and 0.1 μM Methiothepin to block 5HT_3 and 5HT_1 -like receptors respectively. 100 μM Pargyline is also added to the tissues at the start of the experiment. Tissues are left for 15 minutes to equilibrate and then exposed to 5-HT at 0.1 μM every 15 minutes until a uniform response is achieved. Following a half hour period for tissues to stabilise, non-cumulative dose response curves to 5-HT are constructed in all tissues. When base-lines have returned to normal, test compounds are added in the reservoirs of the tissue set-ups and washed in to the tissues. Tissues are incubated with the antagonists for 45 minutes after which a second non-cumulative dose response curve to 5-HT is constructed.

To test for selectivity of action, compounds are tested for their ability to antagonise cholinergically-mediated contractions of the guinea-pig colon, evoked by the nicotinic receptor agonist, DMPP (1,1-dimethyl-4-phenyl-piperazinium iodide). For these experiments, tissues and equipment are set up as for the above, 5HT_4 receptor experiments. After sensitization, non-cumulative dose response curves are constructed to DMPP. Test compounds are incubated with the tissues as above, and a second dose response curve to DMPP created. Results are given as mean $\text{pKB} \pm \text{SEM}$ values for each antagonists.

The compound of formula (I) was found to have a pKB value of 8.47 ± 0.23 (n=7) and did not significantly affect DMPP-evoked contractions.

Claims

1. (±)-N-[(1-Butyl-4-piperidinyl)methyl]-3,4-dihydro-4-hydroxy-2H-
5 [1,3]oxazino[3,2-a]indole-10-carboxamide
i.e. the compound of formula (I), or a pharmaceutically acceptable salt thereof:



- 10
2. A process for preparing a compound of formula (I) according to claim 1 which comprises reacting 1-n-butyl-4-piperidinyl methylamine with (+/-)-methyl 3,4-dihydro-4-(protected)hydroxy-2H-[1,3]oxazino[3,2-a]indole-10-carboxylate.
- 15
3. A pharmaceutical composition comprising a compound according to claim 1, and a pharmaceutically acceptable carrier.
4. A compound according to claim 1 for use as an active therapeutic substance.
- 20
5. The use of a compound according to claim 1 in the manufacture of a medicament for use as a 5-HT₄ receptor antagonist.
6. The use according to claim 5 for use as a 5-HT₄ antagonist in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.
- 25
7. A method of treatment of irritable bowel syndrome, gastro-oesophageal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine in mammals, such as humans, which comprises the administration of an effective amount of the compound of the formula (I) or a pharmaceutically acceptable salt thereof.
- 30

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/07764

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D498/04 A61K31/535 //(C07D498/04,265:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 18036 A (SMITHKLINE BEECHAM PLC) 16 September 1993 cited in the application see claims 1,12-15; example 3 ---	1,3-6
A	L. GASTER: DRUGS OF THE FUTURE, vol. 22, no. 12, 1997, pages 1325-32, XP002099385 see the whole document ---	1,4-6
A	L. M. GASTER ET AL.: JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 24, 1995, pages 4760-3, XP002099386 see table 1, compounds 10 to 12 --- -/--	1,4-6

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

9 April 1999

Date of mailing of the international search report

27/04/1999

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Hass, C

INTERNATIONAL SEARCH REPORT

Interi nal Application No

PCT/EP 98/07764

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	G. A. KENNETT ET AL.: NEUROPHARMACOLOGY, vol. 35, no. 4/5, 1997, pages 707-12, XP002099387 see page 708, right-hand column, paragraph "Materials"; table 2; table 3 -----	1,4-6
A	EP 0 501 322 A (GLAXO GROUP LTD.) 2 September 1992 cited in the application see claims 1,14-16 -----	1,3-6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/07764

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Claims Nos.: 7

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/07764

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